PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14 OCT 2004

Applicant's or agent's file reference 257.P2F	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/12901	International filing date *(day/month/year)* 25.04.2003	Priority date *(day/month/year)* 26.04.2002
International Patent Classification (IPC) or both national classification and IPC C07F9/40		
Applicant GILEAD SCIENCES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.11.2003	05.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Richter, H Telephone No. +49 89 2399-8539

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/12901

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-1646 as originally filed

Claims, Numbers

1-27 received on 15.06.2004 with letter of 15.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 00/04033 A (ARMITAGE IAN GORDON ;SEARLE ANDREW DAVID (GB); GLAXO GROUP LTD (GB) 27 January 2000 (2000-01-27)

D9: WO 02/06292 A (DU PONT PHARM CO) 24 January 2002 (2002-01-24)

D15: XP-001120503 Gatell, J.M.: "From Amprenavir to GW433908" J. HIV Ther. 2001 Nov; 6 (4) 96-96 (copy attached)

D16: NLM11968788 Medline print-out (April 2002) (copy attached)

The documents D1, D9, D15 and D16 are regarded as pertinent prior art to the subject-matter of claim 1, and disclose Amprenavir derivatives having a phosphono group at the position corresponding to R3 of the compounds of formula II according to the application; see D1, compounds (I), (III), (IV) and pages 1-7; D9, page 17 and claims 1-27; and D15, Fig. 2.

The possibility of R3 being phosphono is also included in the definition of present claim 1 (see claim 1, last line "...and prodrugs thereof"). This can be seen from D15, fig. 2 which shows that a prodrug named GW433908 can be made by changing an OH into a phosphoro group. Likewise, the compound of formula I according to D9 is also a prodrug as can be seen from D9, page 21, lines 10-17. Hence, the definition of R3 according to the application includes a phosphono group.

The subject-matter of claim 1 therefore differs from the known prodrugs (disclosed in D1, D9,D15 and D16) in that at least one of the groups A^0 has to include A^1 which contains a phosphorus containing group W^6; see the definition of W^3). Hence, claim 1 is novel as well as the dependent claims 2-27.

The problem to be solved by the present invention was to make available new protease inhibitors which have a reduced tendency to develop resistant strains and which have extended half-life in vivo. These problems are solved by the compounds of claims 1-27 as can be seen from the description beginning at page 1585.

Some advantages of GW433908 over Amprenavir are described in D15, page 97, left hand column, yet there is no clear teaching about the resistance profile of GW433908 until the priority date of the present application; see MEDLINE database printout D16. GW433908 only appears to be on the short list of promising candidates.

Likewise, no prior art could be found concerned with the extension of half-life of GW433908 over Amprenavir.

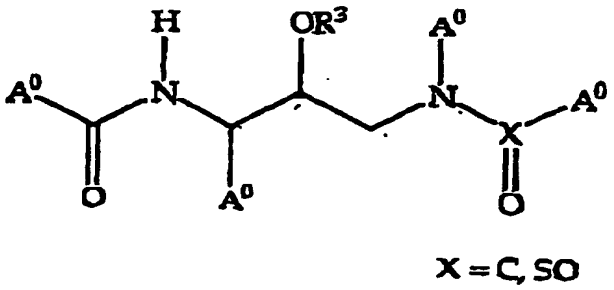
D1 and D9 are concerned with problems different from resistant strains and improved half-life. D9 is only concerned with the design of new HIV drugs and D1 (see page 16) only addresses the oral bioavailability and aqueous solubility.
Hence, D1 and D9 are further away from the invention than D15 and D16.

Claims 2-27 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

The closest prior art according to D15 and D16 is not mentioned in the description and the description is not in line with the scope of the claims.

Claims:

1. A compound of the Formula:



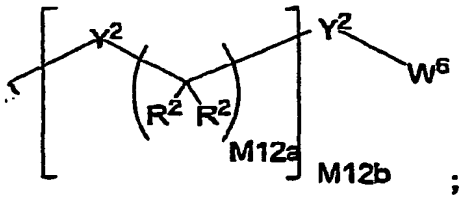
X = C, SO

II

wherein:

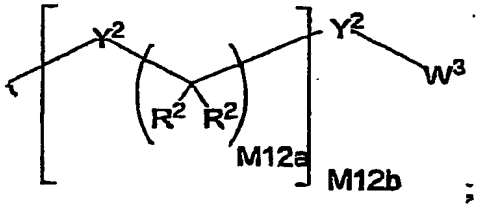
A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

A^1 is:



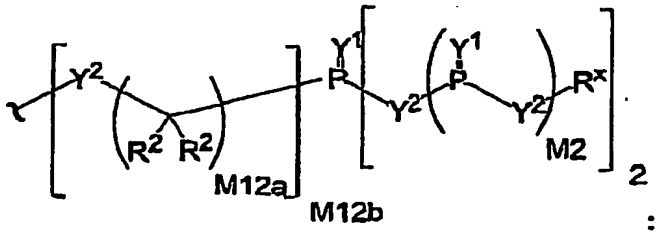
M12a M12b ;

A^2 is:



M12a M12b ;

A^3 is:

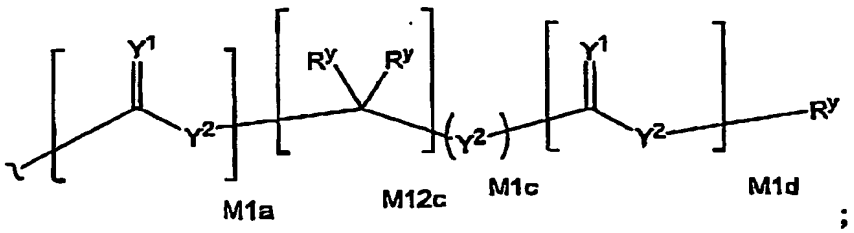


M12a M12b M2 2 :

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups, or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

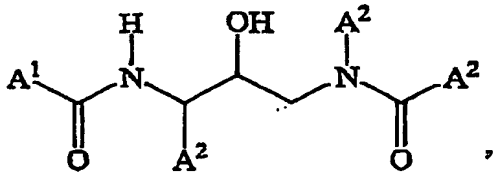
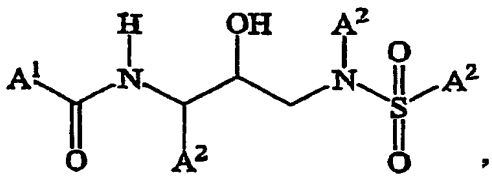
M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

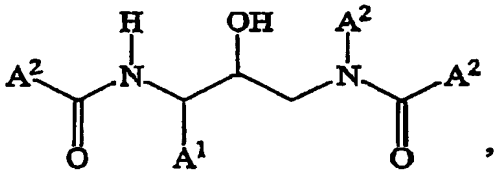
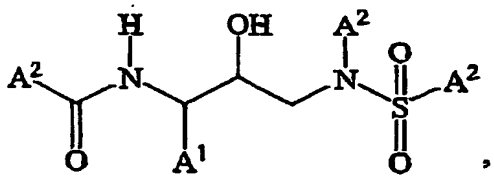
M1a, M1c, and M1d are independently 0 or 1; and

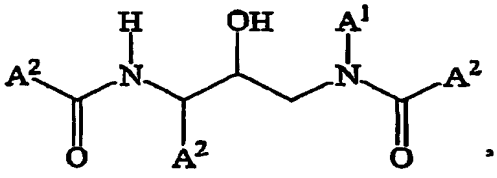
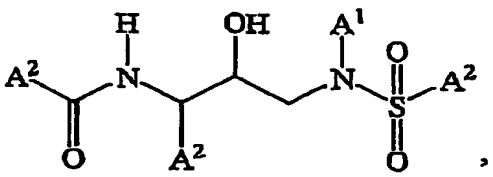
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, and

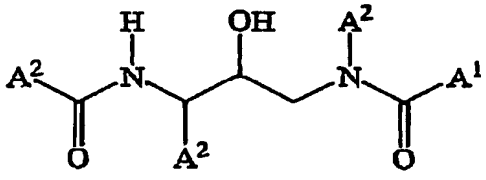
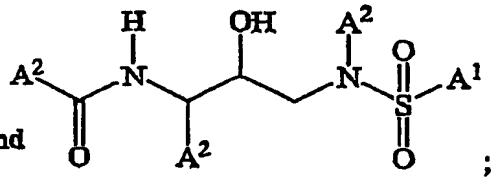
the enantiomers and diastereomers, as well as the physiologically acceptable salts and prodrugs thereof.

2. A compound of claim 1 selected from:

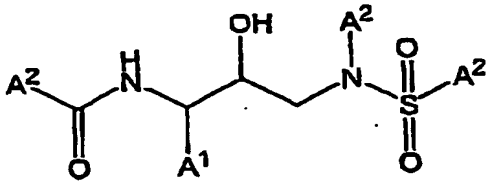

,

,


,

,

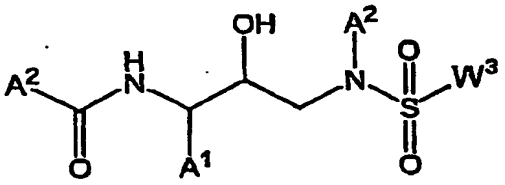

,

,


, and

;

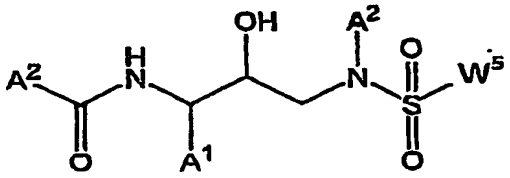
3. A compound of claim 2 having the formula:



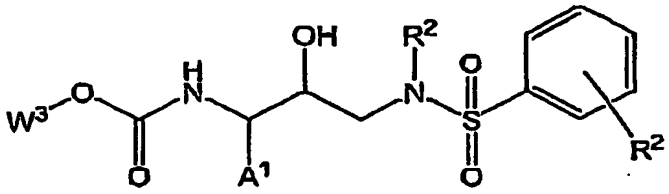
4. A compound of claim 1 having the formula:



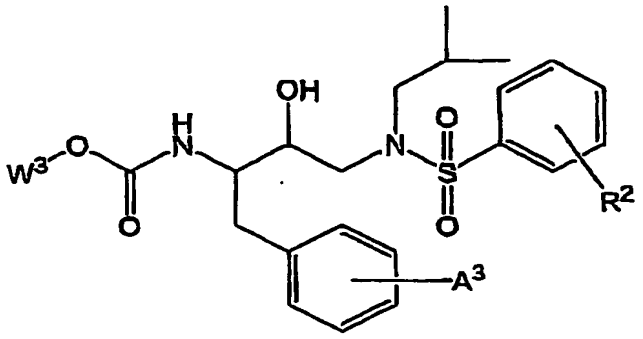
5. The compound of claim 4 having the formula:



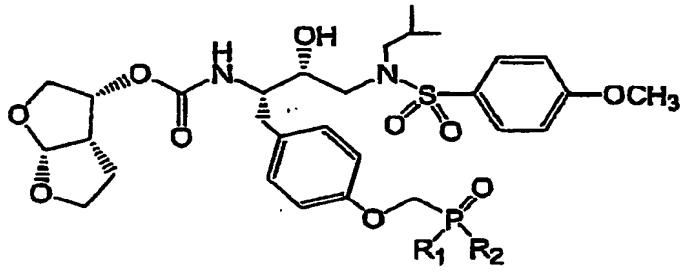
6. A compound of claim 5 having the formula:



7. A compound of claim 6 having the formula:

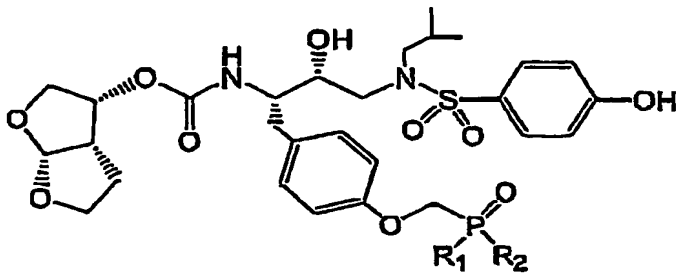


8. A compound of claim 7 having the formula:



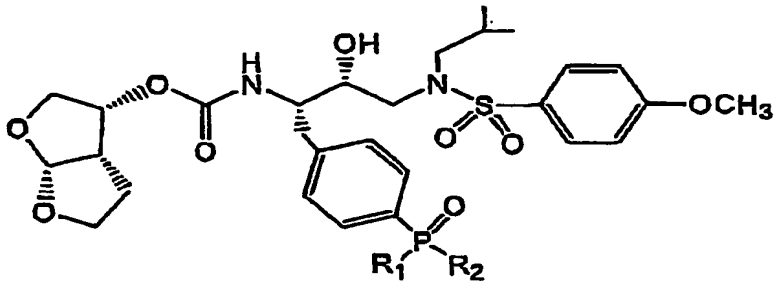
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyl-oxymethyl.

9. A compound of claim 7 having the formula:



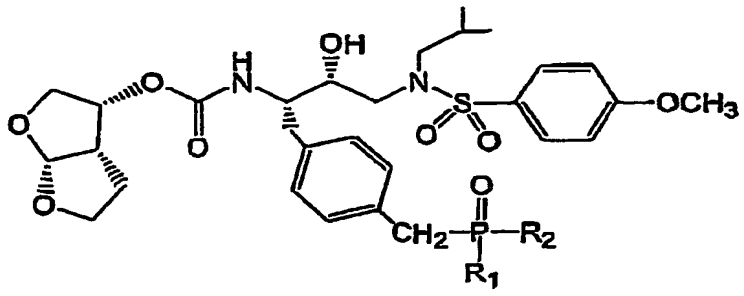
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

10. A compound of claim 7 having the formula:



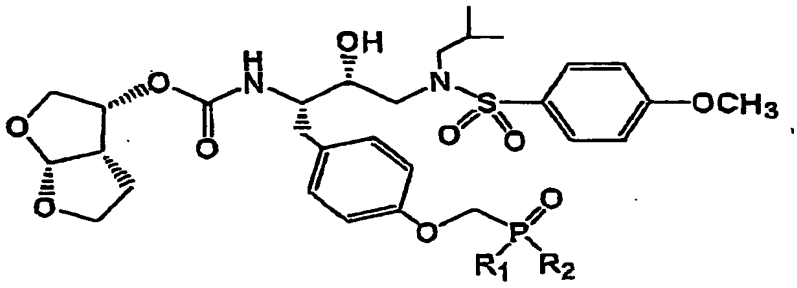
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

11. A compound of claim 7 having the formula:



wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

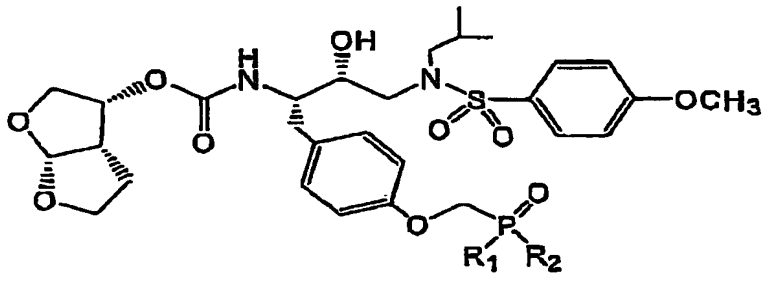
12. A compound of claim 7 having the formula:



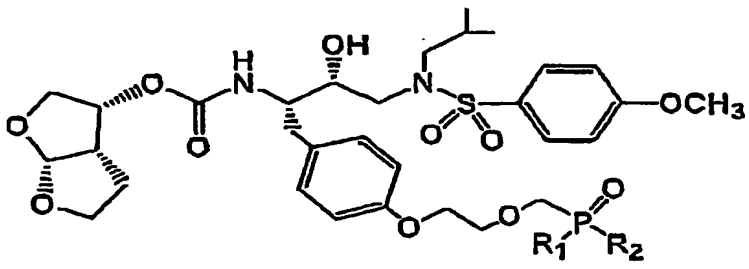
wherein R_1 and R_2 are independently selected from –NR where R is C_1–C_8 alkyl or an amino acid ester.

13. The compound of claim 12 wherein R_1 and R_2 are independently selected from –NMe, -NEt, Gly-Et, Ala-Et, Aba-Er, Val-Et, Leu-Et, Phe-Bu, and Phe-Et.

14. A compound of claim 7 having the formula:



or



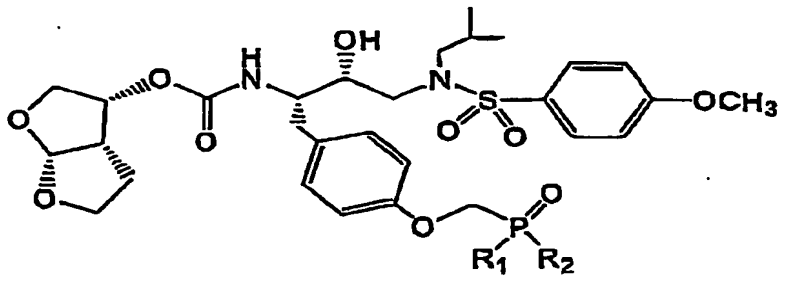
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, and a lactate ester.

15. The compound of claim 14 wherein R_1 is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R_2 is Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et, Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, or DiMePro-Me.

16. A compound of claim 15 where the lactate ester is the (R) configuration.

17 A compound of claim 15 where the lactate ester is the (S) configuration.

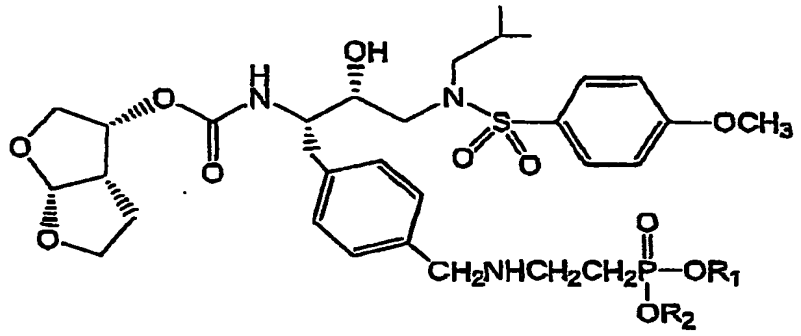
18. A compound of claim 7 having the formula:



wherein R_1 is phenoxy, benzyloxy, ethoxy, trifluoroethoxy, or hydroxyl; and R_2 is an amino acid ester.

19. The compound of claim 18 wherein the amino acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH.

20. A compound of claim 7 having the formula:

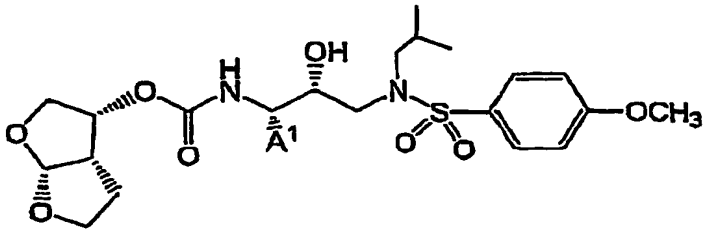


wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxy-methyl, an amino acid ester and a lactate ester.

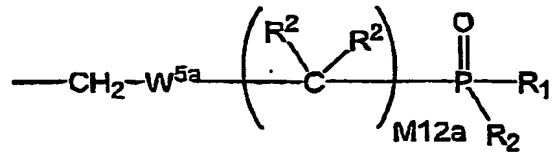
21. The compound of claim 20 wherein R_1 is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R_2 is a lactate ester selected from Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et, Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, and DiMePro-Me.

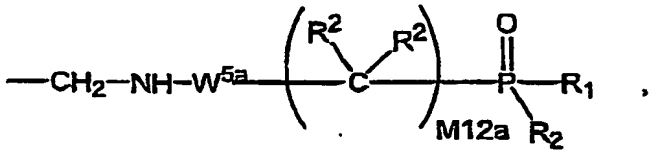
22. The compound of claim 20 wherein R_1 is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R_2 is an amino acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH.

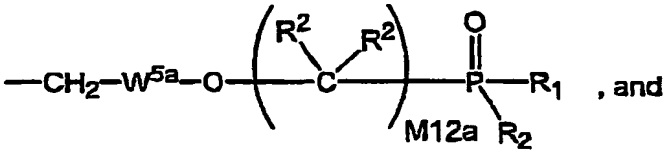
23. A compound of claim 1 having the formula:



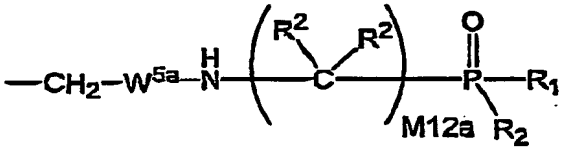
wherein A^1 is selected from the formulas:





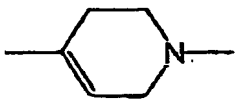


, and

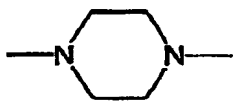


R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, an amino acid ester and a lactate ester; and

W^{5a} is selected from the formulas:



,



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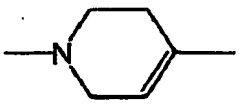

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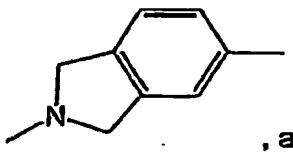
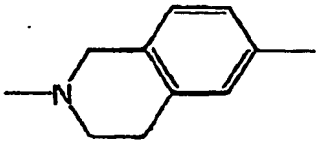
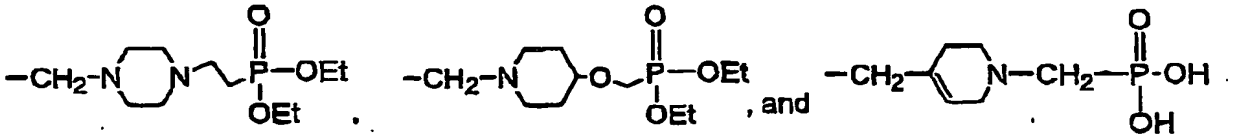


, and



.

24. A compound of claim 23 wherein A^1 is selected from the formulas:



, and

25. The use of a compound according to any one of claims 1 to 24 in the manufacture of a medicament for the treatment of HIV infection.

26. The use of a compound according to any one of claims 1 to 24 in the manufacture of a medicament for the treatment of disorders affecting white blood cells.

27. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 24 and conventional carriers and excipients.